

Rec'd PCT 18 APR 2005

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
29 April 2004 (29.04.2004)

PCT

(10) International Publication Number
WO 2004/035629 A3

(51) International Patent Classification⁷: C08B 37/00, C08L 5/08, A61K 47/36, A61P 35/00

(21) International Application Number:
PCT/EP2003/011239

(22) International Filing Date: 10 October 2003 (10.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PD2002A000271 18 October 2002 (18.10.2002) IT

(71) Applicant (*for all designated States except US*): **FIDIA FARMACEUTICI S.P.A.** [IT/IT]; Via Ponte della Fabbrica, 3/A, I-35031 Abano Terme (IT).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **DE LUCA, Gilda** [IT/IT]; Via Goito 58, I-35100 Padova (IT). **MARINI BETTOLO, Rinaldi** [IT/IT]; Via Crescenzo 58, I-00193 Roma (IT). **MIGNECO, Luisa, Maria** [IT/IT]; Via Pereira 206, I-00136 Roma (IT).

(74) Agent: **GERVASI, Gemma**; Notarbartolo & Gervasi S.p.A., Corso di Porta Vittoria, 9, I-20122 Milan (IT).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
24 June 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/035629 A3

(54) Title: TAXANES COVALENTLY BOUNDED TO HYALURONIC ACID OR HYALURONIC ACID DERIVATIVES

(57) Abstract: The present invention relates to water-soluble taxanes covalently bounded to hyaluronic acid or hyaluronic acid derivatives, and in particular to paclitaxel and docetaxel, useful for the preparation of pharmaceutical compositions to be used in the field of oncology, in the treatment of autoimmune disorders and of restenosis. The invention also relates to the process for preparing taxanes covalently bounded to hyaluronic acid or hyaluronic acid derivatives by direct synthesis between molecules of hyaluronic acid and of taxane or by indirect synthesis by the introduction of a spacer between the hyaluronic acid or hyaluronic acid derivative and the taxane.

Rec'd PCT/ 18 APR 2005

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/11239A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08B37/00 C08L5/08 A61K47/36 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08L C08B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>LUO Y ET AL: "SYNTHESIS AND SELECTIVE CYTOTOXICITY OF A HYALURONIC ACID-ANTITUMORBIOCONJUGATE" BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 10, no. 5, 20 September 1999 (1999-09-20), pages 755-763, XP001041280 ISSN: 1043-1802 cited in the application page 755-756</p> <p>---</p> <p>-/-</p>	1-73

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the International search

22 April 2004

Date of mailing of the International search report

04.05.2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Grassi, D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/11239

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SPARER R. V. ET AL.: "Controlled Release from Glycosaminoglycan Drug Complexes" in "Controlled Release Delivery Systems" 1983 , MARCEL DEKKER , NEW YORK XP009025950 page 107-119 page 112-114 ____	1-73
Y	US 4 851 521 A (DELLA VALLE FRANCESCO ET AL) 25 July 1989 (1989-07-25) column 3, line 12-31 column 7, line 61,62 column 13, line 54-61; claim 17 ____	1-73
Y	US 5 648 506 A (SOON-SHIONG P ET AL) 15 July 1997 (1997-07-15) column 2, line 65 -column 3, line 13 column 4, line 19-36; claim 1; example 3 ____	1-73
X	WO 97/33552 A (LI CHUN ;WALLACE SIDNEY (US); YU DONG FANG (US); WALLACE TECH INC) 18 September 1997 (1997-09-18) page 6, line 15 -page 7, line 13; claims 1,12; figure 1A ____	1-73
A	AKIMA K ET AL: "EVALUATION OF ANTITUMOR ACTIVITIES OF HYALURONATE BINDING ANTITUMORDRUGS: SYNTHESIS, CHARACTERIZATION AND ANTITUMOR ACTIVITY" JOURNAL OF DRUG TARGETTING, HARWOOD ACADEMIC PUBLISHERS GMBH, DE, vol. 4, 1996, pages 1-8, XP002942515 ISSN: 1061-186X page 4 ____	1-73
A	US 5 502 081 A (PRESTWICH GLENN D ET AL) 26 March 1996 (1996-03-26) column 11-12 ____	1-73

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/11239

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claim : 1 (part)

Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and carboxyl groups of the hyaluronic acid by means of a spacer (the group of compounds is not unitary, but could be searched without extra effort).

2. Claim : 1 (part)

Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and carboxyl groups of the hyaluronic acid without spacer.

3. Claim : 1 (part)

Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and OH groups of the hyaluronic acid.

4. Claim : 1 (part)

Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and amino groups of deacetylated hyaluronic acid.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/11239

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
US 4851521	A	25-07-1989	IT	1203815 B		23-02-1989
			IT	1214658 B		18-01-1990
			AT	135713 T		15-04-1996
			AT	227741 T		15-11-2002
			AU	591501 B2		07-12-1989
			AU	5983686 A		26-02-1987
			CA	1341276 C		31-07-2001
			DE	3650501 D1		25-04-1996
			DE	3650501 T2		21-11-1996
			DE	3650776 D1		19-12-2002
			DE	3650776 T2		11-03-2004
			DK	323686 A		09-01-1987
			EP	0216453 A2		01-04-1987
			EP	0696598 A1		14-02-1996
			ES	2001512 A6		01-06-1988
			FI	862878 A ,B,		09-01-1987
			FI	892710 A ,B,		02-06-1989
			FI	892711 A		02-06-1989
			FI	94767 B		14-07-1995
			HU	42512 A2		28-07-1987
			IE	81120 B1		22-03-2000
			IL	79362 A		31-07-1995
			IN	165582 A1		25-11-1989
			JP	2569012 B2		08-01-1997
			JP	62064802 A		23-03-1987
			KR	8701901 B1		21-10-1987
			NO	862734 A ,B,		09-01-1987
			NO	910295 A		09-01-1987
			NZ	216786 A		26-05-1992
			NZ	233045 A		26-05-1992
			PH	25189 A		27-03-1991
			PT	82941 A ,B		01-08-1986
			SG	90006 A1		23-07-2002
			US	4965353 A		23-10-1990
			US	5202431 A		13-04-1993
			US	5336767 A		09-08-1994
			PH	25383 A		03-06-1991
			PH	25382 A		03-06-1991
			PH	25642 A		21-08-1991
			PH	25643 A		21-08-1991
			ZA	8605071 A		30-09-1987
US 5648506	A	15-07-1997	AU	4406793 A		30-12-1993
			WO	9324476 A1		09-12-1993
WO 9733552	A	18-09-1997	AU	735900 B2		19-07-2001
			AU	2580697 A		01-10-1997
			BR	9710646 A		11-01-2000
			CA	2250295 A1		18-09-1997
			CN	1217662 A		26-05-1999
			CZ	9802908 A3		14-07-1999
			EA	2400 B1		25-04-2002
			EP	0932399 A1		04-08-1999
			HU	9903952 A2		28-05-2001
			IL	126179 A		10-04-2003
			JP	2000507930 T		27-06-2000
			JP	2003063960 A		05-03-2003
			NO	984210 A		11-11-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/11239

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9733552	A	NZ 332234 A PL 328807 A1 US 2001034363 A1 WO 9733552 A1 US 2003073615 A1 US 2003114518 A1 US 2003113335 A1 US 2003114397 A1 US 2003114363 A1 US 2003073617 A1 US 2003134793 A1 US 2003130178 A1 US 2003130170 A1 US 2003130341 A1 US 2003147807 A1 US 2003124055 A1 US 6262107 B1 US 2003176320 A1 US 2004018960 A1 US 5977163 A	23-06-2000 15-02-1999 25-10-2001 18-09-1997 17-04-2003 19-06-2003 19-06-2003 19-06-2003 19-06-2003 17-04-2003 17-07-2003 10-07-2003 10-07-2003 10-07-2003 07-08-2003 03-07-2003 17-07-2001 18-09-2003 29-01-2004 02-11-1999
US 5502081	A 26-03-1996	US 5356883 A US 6096727 A US 6537979 B1 US 6013679 A WO 9402517 A1 CA 2022091 A1 EP 0416250 A2 JP 3088802 A	18-10-1994 01-08-2000 25-03-2003 11-01-2000 03-02-1994 02-02-1991 13-03-1991 15-04-1991